REMARKS/ARGUMENTS

Claims 12, 15, 16, 21, 24, 26-33 and 59 are pending in the instant application. Claims 12, 15, 16, 21, 24, 26-33 and 59 have been rejected. Claim 59 has been canceled and the subject matter represented in new claim 60. Claims 28-33 have also been canceled without prejudice. Claims 12, 15, 16, 21, 24, 26 and 27 have been amended. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Rejection of Claim 59 under 365 U.S.C. § 112, first paragraph

Claim 59 has been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for obtaining and using human embryonic stem cells. As pointed out by the Examiner, claim 59 as presented in the amendments of August 6, 2002, May 3, 2002, and September 20, 2001 erroneously contained the phrase "or human" which had been deleted by Applicants in the amendment filed March 28, 2001.

Accordingly, in an earnest effort to advance the prosecution

of this case and to clarify the subject matter being claimed, Applicants have canceled pending claim 59 and represented the invention in new claim 60. New claim 60 is drawn to a method of isolating a pure population of mammalian CNS neuron-restricted precursor cells from a sample of mammalian embryonic stem cells.

Applicants respectfully disagree with the Examiner's suggestion that the specification does not enable one skilled in the art to make and use the invention to obtain and use human embryonic stem cells. The Examiner cites *In re Hogan and Banks*, 194 USPQ 527 (1977) as making clear that enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claims. The Examiner also suggests that the current application claims a priority date of July 4, 1997.

It is respectfully pointed out, however, that the instant application is a continuation-in-part application, the filing date of which is July 2, 1998. Methods relating to mammalian embryonic stem cells were first introduced in this continuation-in-part application. Thus, in accordance with MPEP §201.11, §706.02, and §2133.01, the effective filing date for claim 60 is July 2, 1998. Therefore, it is this date by which the instant

claimed invention must have been enabled.

The test of enablement as set forth in MPEP § 2164.01 is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with information known in the art without undue experimentation.

Embryonic stem cells for mammals other than mice were known in the art and described in the literature prior to July 2, 1998 filing date of this continuation-in-part application. For example, a primate embryonic stem cell line was described by Thomson et al. in August of 1995 (PNAS 1995 92(17):7844-8). In subsequent publications of August 1996 and January 1998, embryonic stems cells from both marmosets and rhesus monkeys were disclosed (Thomson et al. Biology of Reproduction 1996 55(2):254-9; Thomson et al. APMIS 1998 106(1):149-56). Primordial germ cell-derived cells from the pig were also described in 1997 (Piedrahita et al. Journal of Reproduction and Fertility 1997 52:245-54).

In addition, as evidenced by Thomson et al.'s publication in Science of November 1998, human embryonic stem cells had also been identified and were in the process of further characterization prior to the filing date of this patent application.

Accordingly, the starting materials for isolation of CNS neuron-restricted precursor cells from embryonic stem cells of various mammals were available as of the filing date of the present application.

Further, use of this method to isolated CNS neuron-restricted precursor cells from mammalian ES cells other than mice has been confirmed. See, for example, Carpenter et al. (Experimental Neurology 2001 172:383-397) and Mayer-Proschel et al. (Clinical Neuroscience Research 2002 2:58-69) both confirming that CNS neuron-restricted precursor cells can be isolated from human embryonic stem cells in accordance with the method of claim 60 and that exemplified in the instant patent application for mouse embryonic stem cells. See specifically page 391 of Carpenter et al, wherein it is taught that the methods for enriching neural progenitor in human ES cells were the methods taught for mouse in reference 21 (Mujtaba et al. Dev. Biol. 214:113-127). Also see Section 2.2 of Mayer-Proschel et al. at pages 59-60 which sets forth the same method for isolating human CNS neuron-restricted precursor cells from human embryonic stem cells as set forth in claim 60. A

Supplemental IDS including copies of these references is being filed with this amendment to place these references into the record for consideration.

As stated in MPEP § 2164.04, a specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken in compliance with the enablement requirements of 35 U.S.C. § 112, first paragraph, unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support. The specification clearly teaches use of the claimed methods for isolation of additional mammalian CNS neuron-restricted precursor cells than those exemplified herein. See for example, page 18, lines 6-7 of the instant application. Thus, the specification disclosure contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented. Further, the Examiner has provided no reason to doubt the objective truth of statements that these methods can be used to isolate other mammalian CNS

neuron-restricted precursor cells from other mammalian ES cells. In contrast, as shown by Applicants herein, other mammalian ES cells in addition to mouse were clearly available as of the effective filing date of this application. Further, Applicants have provided confirming evidence of the utility of the claimed methods in isolating additional mammalian CNS neuron-restricted precursor cells from mammalian ES cells other than those specifically exemplified in the application.

Accordingly, the instant application meets the enablement requirements of 35 U.S.C. § 112, first paragraph, and withdrawal of this rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

II. Rejection of Claims under 35 U.S.C. § 112, second paragraph

Claim 59 has been rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps. Specifically, the Examiner suggests that an initial differentiation step for obtaining CNS neuron-restricted precursor cells from ES cells is omitted. Further, the Examiner suggests that step (b) is confusing in light of teachings at page 55 of the specification regarding no expression of A2B5 in ES

cells. In addition, the Examiner suggests that were the claims amended to recite a differentiation step, it is ambiguous how differentiation to only "CNS neuron-restricted precursor cells" is achieved, versus continued differentiation to neurons and glial, or more importantly to any other cell type which is not a CNS cell.

As discussed in Section I, *supra*, claim 59 has been canceled and the subject matter represented in new claim 60. New claim 60 includes a step for differentiation by plating mouse embryonic stem cells in neural differentiation conditions so that the ES cells alter their morphology and express neuronal and glial markers nestin, NCAM, MAP2 kinase, GFAP and cyclophilin/DM20/PLA. Support for this step is provided in the specification at page 55, lines 12-15 and Figure 13. Claim 60 also makes clear in step (b) that A2B5+ cells are removed from the differentiated cells of step (a), not ES cells taught in the specification not to express A2B5. Further, this claim addresses any ambiguity with respect to obtaining a pure population of CNS neuron-restricted precursor cells from ES cells. Contrary to the Examiner's suggestion that the present invention involves ES

cells differentiating to only "CNS neuron-restricted precursor cells", claim 60 makes clear that to obtain CNS neuron-restricted precursor cells from ES cells, the step of differentiating mouse embryonic stem cells by plating the cells in neural differentiation conditions so that the ES cells alter their morphology and express neuronal and glial markers nestin, NCAM, MAP2 kinase, GFAP and cyclophilin/DM20/PLA, is followed by removing A2B5+ cells from the differentiated cells; purifying from supernatant a subpopulation expressing embryonic neural cell adhesion molecule, plating the purified subpopulation of cells in feeder-cell-independent culture on a substratum and in a FGF-containing medium, and incubating the plated cells in the FGF-containing medium to obtain an isolated, pure population of mouse CNS neuron-restricted precursor cells. is achieved, versus continued differentiation to neurons and glial, or more importantly to any other cell type which is not a CNS cell. Thus, claim 60 leaves no ambiguity with respect to how the CNS neuron-restricted precursor cells are obtained.

Withdrawal of this rejection under 35 U.S.C. § 112, second paragraph is therefore respectfully requested.

Claims 12, 15-16, 21, 24, 26-33 and 59 have also been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject mater which applicant regards as the invention. Specifically, the Examiner suggests that it is unknown what metes and bounds exactly constitute or differentiates "adherent growth supporting medium" from "retinoic acid containing medium" from "astrocyte promoting medium" from "feeder-cell-independent culture" from "proliferating conditions" from "differentiation conditions". The Examiner suggests that the metes and bounds of "plated at a temperature and in an atmosphere conducive to growth" are also unknown.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended the claims to remove the phrases "adherent growth supporting medium", "retinoic acid containing medium","astrocyte promoting medium", "proliferating conditions" and "differentiation conditions".

With respect to the phrase "feeder-cell-independent culture", Applicants respectfully disagree with the Examiner regarding its indefiniteness. As taught in MPEP § 2173, definiteness of claim language must be analyzed, not in a vacuum, but in light of:

(A) The content of the particular application disclosure;

(B) The teachings of the prior art; and

(C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. The specification at page 16, lines 1-11, defines what is meant by use of "feeder-cell-independent adherent culture" in the instant invention. Thus, what is meant by this phrase is quite clear when read in light of the content of this application disclosure as required by MPEP § 2173.

Accordingly, withdrawal of these rejections under 35 U.S.C. § 112, second paragraph is respectfully requested in light of the amendments to the claims and the above remarks.

Claims 15 and 16 have also been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner suggests that there is no antecedent basis for "said procedure" in claim 15 or "said mammalian" in base claim 12.

With respect to claim 15, Applicants respectfully disagree since step (e) of claim 12 states that purifying a subpopulation

of cells expressing embryonic neural cell adhesion molecules is performed "via **a procedure** selected from the group consisting of . . . ".

However, in an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 to clarify that the subpopulation of cells expressing embryonic neural cell adhesion molecules is purified by specific antibody capture. Claim 24, which depends from claim 21 has been amended in similar fashion. Applicants have also amended claim 16 to replace the term "mammalian" with --rodent or human--.

Withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is therefore respectfully requested.

III. Rejection of Claims 26 and 27 under 35 U.S.C. § 102(b)

The rejection of claims 26 and 27 under 35 U.S.C. § 102(b) as being anticipated by Blass-Kampmann et al. (1994) has been maintained for reasons made of record in Paper Nos. 5, 10 and 22. In Paper No. 10 (Office Action mailed May 24, 2000), the Examiner rejected claims 26 and 27 suggesting that argument presented by Applicants detailing the distinguishing

characteristics of the cells of the instant invention from the cells of Blass-Kampmann et al. were not persuasive because the method steps recited in the claims which produce the cell of the instant invention are not distinguishable over the prior art method steps. In Paper No. 22 (Office Action mailed , the Examiner re-instated the rejection of these claims under 35 U.S.C. § 102(b) suggesting that the claims did not distinguish the instant invention from the method of Blass-Kampmann et al. because no antibody directed toward a sialyated form of NCAM was required. Applicants respectfully traverse this rejection.

Contrary to the Examiner's suggestions, the method steps of claims 12 and 21, from which claims 26 and 27 depend respectively, are clearly distinguishable from the teachings of Blass-Kampmann et al. Both claims 12 and 21 explicitly state in step (c) that A2B5+ cells are removed from the dissociated cells via specific antibody capture with an antibody that specifically recognizes A2B5. This step is neither taught nor suggested in the teachings of Blass-Kampmann et al. Further, no such removal step was conducted by Blass-Kampmann et al. since this reference teaches that their RB21-7+ astrocytes contained glial precursors and/or bipotential cells and exhibited early morphological

diversification into glial-fibroblast-like and neuronal shapes. See page 365 of Blass-Kampmann et al.

Further, claims 12 and 21 both require in step (e) and (d), respectively, that an antibody that specifically recognizes polysialated neural cell adhesion molecule be used. Accordingly, the Examiner's suggestion that no antibody directed toward a sialyated form of NCAM is required is also incorrect.

Accordingly, withdrawal of this rejection of claims 26 and 27 under 35 U.S.C. § 102(b) is respectfully requested.

IV. Rejection of Claims 26-28, 29, and 32-33 under 35 U.S.C. § 102(e)

Claims 26-28, 29 and 32-33 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Boss et al. (U.S. Patent 5,411,883). The Examiner suggests that Boss et al. teach a method of using differentiating conditions to obtain postmitotic neurons which includes addition of the neuronal maturation factor, retinoic acid (i.e. as it relates to claims 29 and 32-33. Further, the Examiner suggests that Boss et al. teaches method of obtaining pure populations of neurons-restricted precursor cells using FACS or magnetic bead sorting (e.g. column 12, lines 54-61

and column 19, lines 29-30) as it relates to claims 26-27 and 28.

Applicants respectfully traverse this rejection.

The Examiner suggests that this rejection of the method claims may be obviated by amending claim 28 to recite that the pure population of neuron-restricted cells is obtained by the method of claim 12. It is respectfully pointed out that claims 26 and 27, which are included in this rejection, are already dependent from method claims 12 and 21, neither of which are taught by Boss et al. Further, no specific application of the Boss reference to these claims has been provided by the Examiner. Thus, inclusion of claims 26 and 27 in this rejection appears to be in error.

With respect to claims 28, 29, and 32-33, Applicants have canceled these claims without prejudice, thus mooting this rejection as it pertains to these claims.

Withdrawal of this rejection under 35 U.S.C. 102(e) is therefore respectfully requested.

V. Conclusion

Applicants believe that this submission overcomes all pending rejections in this case and comprises a full and complete

response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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